Author's response to reviews

Title: Late HBsAg seroreversion of mutated Hepatitis B virus after bone marrow transplantation

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Author's response to reviews: see over
Ulm, 2nd May.2013

Dear Dr. Harris

We thank the reviewers for their detailed comments and questions which have all been addressed in the submitted revised version of our manuscript as you may see also from the following (see next page) point to point answers.

We believe that by following the reviewers instructions the manuscript has been substantially improved and hope that it is now regarded suitable for publication in BMC Infectious Diseases.

Sincerely

Th. Mertens
Reviewer: Valentina Stosor

1. The authors state that hepatitis HBcAb positivity is a frequent event in patients with hematologic malignancies and greater than age 60 years. The authors should clarify the statement by providing estimates of seroprevalence in their region.

In the original manuscript we had meant that elderly patients are more frequently positive for serum markers of a resolved HBV infection. The statement was not clear, therefore we rephrased the paragraph and in addition added epidemiological data about the age dependent prevalence of HBV markers in the German population and resolved HBV infection in Europe [1].

2. The authors should report on the hepatitis B serostatus of the stem cell donor.

AND

3. The authors should comment on the contribution of donor immunity to the development of hepatitis B seroreversion.

We included the information about the Hepatitis B serostatus of the stem cell donor, who was HBsAb negative as a non responder after HBV vaccination, and added a general comment on the donor immunity as a factor in HBV seroreversion.

Reviewer: Sarah Hammond

1. The authors spend time discussing seroreversion (also termed “reverse seroconversion” in HSCT literature) in all patients receiving immunosuppression and report a vast range of incidences. It is worth noting that this is a heterogeneous group which includes patients receiving therapy for lymphoma with and without rituximab as well as HSCT recipients. It is not surprising that the risk is highly variable among these different types of patients. Since this case report is about an HSCT recipient this reviewer suggests that the introduction and discussion focus on seroreversion in HSCT recipients only. The risks for seroreversion have been studied previously specifically in this population.

The reviewer is right in noting that the group at risk is a very heterogeneous group. In the revised version of our manuscript we have focused on HBsAg seroreversion in HSCT recipients. We rephrased the respective paragraphs and tried to specify on this without increasing the length of our manuscript. We have included and discussed a number of additional publications in the revised manuscript.

2. However, the most critical issue with the introduction and discussion of this case report is that the literature review is inadequate. The authors rely on several publications (many case reports) that assess HBV reactivation in a small number of HSCT recipients with previously resolved infection (seroreversion/reverse seroconversion) to draw several conclusions (references 1-5, 12, 15, 16, 18--> reference 17 is a duplicate of #3)

We have included the references suggested by the reviewer and rephrased the manuscript accordingly. We apologize for our mistake in citing references 3 and 17.

Specific points:
• Introduction: “Nevertheless, taking in to consideration. . . the risk of HBV seroreversion may still reach 100%”
As mentioned above, we have now included more published data in the introduction and discussion and corrected the manuscript. On the other hand Knöll et al.[3] wrote: In conclusion, the risk of reactivation of a resolved HBV infection is close to 100% in allogeneic stem cell recipients.

- Conclusions: “...no well-defined risk factors for HBV seroreversion in patients with previously resolved HBV infections are available in the literature”
- Conclusions: “Interestingly, according to the literature, patients with...then those who are only HBcAb-positive.”

We have further described the main risk factors for seroreversions that have been presented and discussed in the literature with respect to risk groups. Specifically, different immunosuppressive drugs and treatment regimens, different underlying onco-hematological diseases before HSCT or GvHD occurrence after HSCT, time after HSCT with ongoing immunosuppression [4,6,15-19], donor immunity against HBV and the amount of HBsAb in the recipient [3,14].

4. One point of interest would be whether the donor was vaccinated against HBV before donation or the recipient was vaccinated for HBV after HSCT-- Knoll, et al. suggest that the escape mutant detected in their cohort may have resulted from donor pretransplant vaccination.

We included the information about the Hepatitis B vaccination and serostatus of the stem cell donor (see above).

5. The point that the authors conclude with about the questions of prophylaxis duration is a keen observation given the timing of reactivation in this patient.

We have rewritten this section and have made it clear now that no evidence based recommendations for prophylaxis with antiviral agents can be given now, especially concerning duration of therapy.